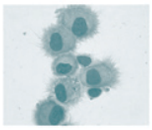
Human Vaccines & Immunotherapeutics



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From rubella to rotavirus, and beyond

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It was customary for medical students with some ambition to seek their way to a biomedical research group. I was intrigued by viruses, and virology was one of the few subjects in medical school that I studied with real interest. Next, in late 1966, I was incredibly lucky to meet Antti Vaheri (later Professor of Virology) who had just returned to Finland from the Wistar Institute in Philadelphia with all the latest knowledge in rubella research. Rubella virus hemagglutination had been discovered and with hemagglutination inhibition (HI) test available I was soon running a diagnostic rubella laboratory which not only provided material for research but also created real income for the Department and our group. This set a precedent for my later professional life. Grants are good but it is better if the research funding can be obtained from outside.

We developed the first rubella IgM test for the diagnosis of recent infection by separating the 19S (IgM) and 7S (IgG) antibodies using ultracentrifugation and testing the fractions using HI test. This was the mother of all IgM antibody diagnostics, and became a Citation Classic by Current Contents. The rubella IgM test also opened the door to my later work in New York, in Dr. Louis Z. Cooper's (originally Professor Saul Krugman's) Rubella Project in the years 1972–1975. But before this I made my first contact with vaccine research.

Live attenuated rubella vaccines were being developed and the leading candidate was HPV-77 high passage virus from NIH. An important open question was whether the live attenuated vaccine would cross placenta same way as wild type rubella virus. The crucial study was to be done in Finland, away from potentially damaging publicity in the US, with Dr. Fred Robbins, a Nobel Laureate, as the godfather of the project. Under the seniors I was to do much of work: vaccinate pregnant women prescreened to be seronegative for rubella and scheduled to have a legal abortion a week or two later. The plan was to isolate rubella (vaccine) virus from the products of conception and, in fact, we succeeded in doing that.

Consequently I got an opportunity to attend an international conference on rubella vaccination in Bethesda, MD, in February 1969. This was an eye opener in many ways. I quickly realized that vaccine research was as much about science as it was about politics. The most impressive spectacle of the conference was Stanley Plotkin's presentation on the RA 27/3 candidate rubella vaccine grown in WI-38 human fibroblast cells. By all accounts, immunogenicity and safety, RA 27/3 appeared superior to HPV77 and its derivatives, but the number of case histories of vaccinated subjects fell short of the required 5000 and the licensure of the "official candidate" HPV77 was on its way. The unholy alliance of NIH and Merck had done everything for the HPV77/DE5 (five passages in duck embryo cells at Merck) vaccine to be ready for licensure in May 1969, with millions of doses already produced to saturate the market immediately. As a token sign for open competition also a Belgian vaccine, Cendehill strain by Jan Desmyter, was granted licensure, but had no real chance in the US market. - As an epilogue, RA27/3 was later adopted by Merck and other manufacturers in 1978 to be included in MMR vaccine.

My time in New York in 1972–1975, first with New York University of rather Bellevue Hospital and then at the Roosevelt Hospital affiliated with Columbia was highly interesting, pleasurable and educational, but not very productive as I was pretty much

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About Dr Vesikari

Dr Timo Vesikari obtained his MD and PhD in Medical Sciences from University of Helsinki in Finland in 1969 and 1972, respectively. From 1972-1975 he performed postdoctoral studies in New York at Bellevue Hospital and Roosevelt Hospital.

His appointments at University of Tampere include Professor of Pediatrics in 1981-7 and Professor of Virology in 1991-2012, and he was Director of its Medical School in 1995-2001, where he serves as Director of the Vaccine Research Center. Dr Vesikari worked with the Diarrheal Disease Control Program of the World Health Organization (WHO) in 1987-90 and subsequently served on WHO Steering Committees on Diarrheal Disease Vaccines and on Epidemiology and Field Research.

Dr. Vesikari's research interest has focused on vaccine studies since the first rubella vaccine trial in Finland in 1968. From the 1980's to present he performed research on varicella vaccines, but his major interest over the past 30 years has been rotavirus diarrhea and vaccine. He conducted the first clinical trials of live oral rotavirus vaccines in humans in 1982-3, followed by several other rotavirus candidate vaccines. He continued to work with the recent rotavirus vaccines of GSK and Merck, being the principal investigator of the first pediatric trials of Rotarix vaccine and the lead investigator of the Merck's RotaTeq vaccine trial REST, with over 70.000 subjects enrolled in Finland and the US. Dr. Vesikari has conducted clinical trials on many other vaccines for children, including live attenuated and adjuvanted inactivated influenza vaccines, MMRV vaccines, pneumococcal conjugate vaccines and meningococcal vaccines.

During the course of his career Dr Vesikari published about 300 articles in peer-reviewed journals, more than half of which were on diarrheal diseases and rotavirus vaccine. In 2007 Dr Vesikari received the Lancet's "Paper of the Year" award for the publication of the Rotarix and RotaTeq Phase 3 trial data.

Dr Vesikari is an active member of many national and international societies and councils. In 1990 he was Bill Marshall lecturer of the European Society for Pediatric Infectious Diseases (ESPID), and in 2004 organized the ESPID Meeting in Tampere. Dr Vesikari has served on advisory boards of several companies, including Merck, GSK, Sanofi Pasteur, Novartis and MedImmune. He has also helped to organize several European Expert Meetings on Rotavirus Vaccination, and is regularly invited to present at national and international vaccine conferences.

alone running a small laboratory. I learned a lot about cell-mediated immunity, then a new and emerging area. I mentored a thesis work of a visiting scientist, Güler Kanra, and made a lifelong friendship with the future Professor of Pediatrics at Hacettepe University in Ankara, with frequent connections to Turkey. Another long-lasting friendship was with my technician Tom Byrne. I will always remember his maxim "this is so simple that even a doctor can do it". I learned to appreciate many things in the US, first of all that the eminent position in science was based on hard work and long hours, which I often mention to younger colleagues in Finland.

On my return to Finland rubella was no longer a hot topic. I did my pediatric residency and reached for new topics. In the new medical school of the University of Tampere we learned about the recently discovered rotavirus and started doing diagnostic work using electron microscopy in 1976. The next year together with Markku Mäki (later Professor of Pediatrics) we started a prospective surveillance on the etiology of acute gastroenteritis in children and found out that rotavirus was responsible for 54% of hospital admissions and the rotavirus season was from December to June. This information was essential for the first rotavirus vaccine efficacy trial.

I had met Francis André in 1977, and we became good friends until his passing , in 2014. Francis was the Scientific and Medical Director of a Belgian company RIT, later to become SmithKline-RIT, SB, and finally GSK. The CEO of the company was Stan Huygelen, a veterinarian, who had interest in animal diseases and had acquired a calf rotavirus strain NCDV for passaging in cell culture (human rotavirus could not be grown then) and for eventual development as a veterinary vaccine. But there was also cross-reactivity between human and animal group A rotaviruses. George Zissis tested the NCDV, now designated as RIT4237, in gnotobiotic pigs and found that previous administration of the "vaccine" protected against challenge by two human rotaviruses.

The next logical thing to do was to start human studies. Francis André gave us some doses of RIT4237 to give to human adult volunteers, including swallowing it myself. There were no symptoms, but there was not much of an immune response either, due to pre-existing antibodies. We proceeded to children and observed immune responses but still no symptoms. Encouraged, we went on to a quick (not dirty) efficacy trial in 8–11 month-old infants of RIT4237 one dose vs. placebo with follow-up from January to May 1983. When analyzing the data with my younger colleague Erika Isolauri (later Professor of Pediatrics herself), we noticed that we had fewer cases in the vaccinated group, but the results were clearer when we looked at the clinical presentation of the cases so that we introduced the term "clinically significant diarrhea", and against this end point the vaccine had

conferred 90% protection. - Later, with Tarja Ruuska, we devised a numerical score to assess clinical severity more objectively. This has become known as "Vesikari score", and many people know my name from it.

I knew we had something good and important at hand, a kind of first in the world. With Francis André we designed 17 protocols of which 10 were carried out in Tampere, Finland, in the next three years, to cover all areas of rotavirus vaccine, and we pretty much succeeded in learning more about rotavirus vaccine and vaccination than others found in the next 15 years. The idea was, vis-a-viz the rubella vaccine experience, to succeed this time and have a European vaccine licensed and used.

Reviewing what happened helps to understand how the attitudes have changed. In Europe, the main obstacle was lack of data: the significance of rotavirus disease was not much known or appreciated outside Finland, and few people or countries were interested in the vaccine. As it has turned out to be in the 2000's, every country will need to do its own epidemiology and health economics before considering a new vaccine, such as rotavirus.

Globally, the reception by the WHO came as a disappointment. The attitude of the WHO's Diarrhoeal Disease Control (CDD) Programme was generally negative. It was only later that I realized the reason was that ours was the wrong vaccine. The American dominated CDD was determined to suppress a European vaccine to pave way for US competitors which were forthcoming but late. The cited reasons were, among other things that the vaccine should be 100% efficacious against all rotavirus diarrhea and not only efficacious against severe disease – an unrealistic requirement that no rotavirus vaccine has met or will ever meet. The vaccine should also be efficacious in developing countries – a reasonable requirement, which actually was met if severe rotavirus diarrhea was the end point. Even if RIT4237 vaccine was not perfect it was easy to produce and could have made a big difference if introduced in the late 1980's. I still feel sad about thinking how many lives could have been saved over twenty years or so if the first oral rotavirus vaccine had been put in field use with the same vigor as oral rehydration solution in those times.

I joined the WHO CDD Programme for a couple of years (1987–1990). The experience was mixed. It was great to have opportunity of traveling the then exotic countries and work on various studies. Most of my connections with developing countries in Asia and also Latin America are from that time. Within the organization, it was disappointing to see how little academic research or credentials earned in research were appreciated. When the CDD Programme was running out steam and most of funding it was time to leave.

After my return to Finland I became Professor of Virology and retained my position as a Head of Pediatric Infectious Diseases at the Tampere University Hospital. I like to call myself with a line borrowed from Luis Avendaño (who worked for a time at NIH), "The best virologist among pediatricians and the best pediatrician among virologists".

For a quarter of century I have been a proponent of rotavirus vaccination in a generic way, working with all vaccines and vaccine manufacturers. I had a good working relationship with Wyeth on RotaShield vaccine, although I always complained about its high reactogenicity (intussusception was not yet known). Together with the vaccine's developer, Al Kapikian of NIH, we conducted a study on neonatal administration of RotaShield and showed that at this age the vaccine was safe. Neonatal vaccination was successfully applied in a recent study in Ghana, in an attempt to resurrect the RotaShield vaccine for use in developing countries after withdrawal in 1999 for intussusception. I worked with Al Kapikian on this project until his death in 2014. My advice to Wyeth in the early 1990's was to launch rhesus-based RotaShield first as a temporary solution but replace it later with a bovine-human reassortant vaccine (also developed at NIH), which unfortunately did not happen.

Collaboration with Merck on their bovine-human reassortant vaccine RotaTeq®, specifically carrying out a major portion of the REST study, occupied several years of almost full-time activity, and was gratifying as this vaccine was eventually licensed in 2006. The publication of the REST study was also a major milestone as it heralded the new coming of rotavirus vaccination with two new vaccines, RotaTeq® and the human rotavirus vaccine Rotarix™ by GSK. I also worked on the latter since its first clinical protocol in 2000.

The REST study enabled me to establish a network of vaccine trial clinics around Finland. The network, collectively part of the Vaccine Research Center of the University of Tampere, is now well known among vaccine manufacturers. In addition to Merck and GSK, I have worked with Sanofi Pasteur, SP-MSD, Novartis, Pfizer, Baxter, MedImmune and others (some companies no longer exist) and the vaccines have included influenza, varicella, zoster, MMR-V, pneumococcal conjugate, meningococcal vaccines, hexavalent combination vaccines, and many others. Since about 2000, I have been more or less a professional vaccinologist. In general, the relationship with industry has worked well both ways. It is gratifying to be the Lead Investigator for good vaccines and see their way to licensure and implementation with actual impact and benefit to children. In addition to rotavirus, such vaccines include varicella vaccine, intranasal influenza vaccine and meningococcal group B vaccine. Reciprocally, many vaccine manufacturers have probably benefited from close collaboration and communication with an experienced academic investigator. At least this is how it was until recently when large multinational CRO companies have been outsourced to do much of clinical vaccine research for the manufacturers, by which the genuine two-way communication has suffered.

The clinical vaccine trial organization within the University has over the years created surplus which I have been able to use for research. The Vaccine Research Center has included laboratory component for over 20 years. In the 1990's with Xiao-Li Pang we discovered that noroviruses were a significant cause of acute gastroenteritis in children, actually more common than rotaviruses if mild cases were counted. This was the background for the general idea of vaccinating young children against noroviruses.

Since the licensure of oral rotavirus vaccines in 2006 we have been working on non-live rotavirus vaccine and norovirus vaccines, preferably in combination.

While I do not do active laboratory work with my own hands any more, I have a nice group of investigators supervised by Vesna Blazevic, a close coworker. The norovirus components of the vaccine are based on virus like particles (VLPs). The rotavirus component is VP6 protein which, when produced in baculovirus-insect cell system, self assembles to form small rod-like structures. VP6 is my old obsession since the early vaccine trials in the 1980's, when Lennart Svensson showed from our post-vaccination sera that most of the antibody response was against VP6, an antigen which was not appreciated because the antibodies raised against it were non-neutralizing. It now appears that VP6 alone may actually induce protective immunity.

Now that I am retired from my professorship and no longer engaged in teaching or hospital work I am actually able to devote more time to research than before. I certainly hope to remain active in the coming years to be able to carry through clinical trials of our norovirus VLP – rotavirus VP6 combination vaccine.

My zodiac is Gemini. In my professional life I have always had two sides, like basic and clinical research, or virology and pediatrics. The balance may have tilted at times, but I have always been happy to have both of them, and the feeling is only reinforced when I talk to my colleagues who are locked in one subject only. Sometimes the course of events has not been clear at once. I had mixed feelings in 1975 on return from New York to Tampere, to this new Medical School with insufficient facilities, but then in a few years realized that luck had been on my side. I was able to start a significant career in pediatrics, which in turn opened entirely new avenues to me. Likewise, the return in 1990 from Geneva to Finland was a jump to some uncertainty, but then again turned out to be a strike of luck as I could obtain a tailor made position combining virology and pediatrics, leading to the creation of Vaccine Research Center and a new balance between clinical and basic. A comfortable position.